

## University of Groningen

### Headache

de Groot, Femke M.; Voogt-Bode, Annieke; Passchier, Jan; Berger, Marjolein Y.; Koes, Bart W.; Verhagen, Arianne P.

*Published in:*  
JOURNAL OF MANIPULATIVE AND PHYSIOLOGICAL THERAPEUTICS

*DOI:*  
[10.1016/j.jmpt.2011.04.007](https://doi.org/10.1016/j.jmpt.2011.04.007)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2011

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

de Groot, F. M., Voogt-Bode, A., Passchier, J., Berger, M. Y., Koes, B. W., & Verhagen, A. P. (2011). Headache: The placebo effects in the control groups in randomized clinical trials; An analysis of systematic reviews. *JOURNAL OF MANIPULATIVE AND PHYSIOLOGICAL THERAPEUTICS*, 34(5), 297-305.  
<https://doi.org/10.1016/j.jmpt.2011.04.007>

#### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

#### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

# HEADACHE: THE PLACEBO EFFECTS IN THE CONTROL GROUPS IN RANDOMIZED CLINICAL TRIALS; AN ANALYSIS OF SYSTEMATIC REVIEWS

Femke M. de Groot, BSc,<sup>a</sup> Anniëke Voogt-Bode, BSc,<sup>b</sup> Jan Passchier, PhD,<sup>c</sup> Marjolein Y. Berger, MD,<sup>d</sup> Bart W. Koes, PhD,<sup>e</sup> and Arianne P. Verhagen, PhD<sup>f</sup>

## ABSTRACT

**Objective:** The purpose of this study is to describe the effects in the placebo and “no treatment” arms in trials with headache patients.

**Method:** This is a secondary analysis of randomized controlled trials from 8 systematic reviews and selected trials with a “no treatment” or placebo control group. The different types of “no treatment” and placebo interventions were assessed and classified into 6 subgroups. The analyses were carried out according to type of outcome variable.

**Results:** In total, 119 studies were included (7119 participants). The mean recovery rate in all control groups was 35.7%. Significantly more participants recovered in control groups of pharmacological studies than in nonpharmacological studies: 38.5% vs 15.0%, respectively. Adults were more likely to recover in nonpharmacological studies and children in pharmacological studies.

**Conclusions:** The mean recovery rate in the control groups was 36%. The recovery rate varied substantially between type of intervention and patients. (*J Manipulative Physiol Ther* 2011;34:297-305)

**Key Indexing Terms:** *Headache; Placebo Effect; Randomized Control Trial*

**H**eadache is a frequently heard complaint in general practice.<sup>1</sup> The lifetime prevalence of headache in women and men is 95% and 90%, respectively.<sup>1</sup> Two of the most common types of headache are tension-type headache (TTH) and migraine. Tension-type headache

has a 1-year prevalence of 63% in the general population,<sup>1</sup> and migraine has a prevalence of 0.5% to 13.6% in children and adolescents.<sup>2</sup> In adults, the 1-year prevalence of migraine is 17% in women and 6% in men.<sup>3</sup> The prevalence increases by age; most cases start before the age of 20 years,<sup>2</sup> although 23% of the children were migraine free before the age of 25 years, and around the age of 50 years, more than half of the migraine group still had migraine attacks.<sup>4</sup> Headache has a high socioeconomic impact, and it greatly influences quality of life.<sup>5,6</sup> Because of the symptoms, daily activities, family, work, and social contacts can be disturbed.<sup>6</sup>

There are many studies describing the effect of treatment in patients with migraine and TTH. Treatment can consist of pharmacological or nonpharmacological interventions. Pharmacological treatments can be divided into acute or prophylactic medications; nonpharmacological treatments are mostly behavioral interventions like relaxation therapy, cognitive therapy, electromyographic (EMG) biofeedback, or physiotherapy.

The criterion standard to investigate the efficacy of medication or other therapies is a randomized controlled trial (RCT). Different kinds of control groups are used in these studies. Placebo controls are often used in

<sup>a</sup> Medical Student, Department of General Practice, Erasmus Medical Center, Rotterdam, The Netherlands.

<sup>b</sup> Medical Student, Department of General Practice, Erasmus Medical Center, Rotterdam, The Netherlands.

<sup>c</sup> Professor, Department of Clinical Psychology, VU University Amsterdam, Amsterdam, The Netherlands.

<sup>d</sup> Professor, Department of General Practice, University Medical Centre of Groningen, Groningen, The Netherlands.

<sup>e</sup> Professor, Department of General Practice, University Medical Centre of Groningen, Groningen, The Netherlands.

<sup>f</sup> Assistant Professor, Department of General Practice, Erasmus Medical Center, Rotterdam, The Netherlands.

Submit requests for reprints to: Arianne P. Verhagen, PhD, Erasmus Medical Center, Department of General Practice, PO Box 2040, 3000 CA Rotterdam, The Netherlands (e-mail: [a.verhagen@erasmusmc.nl](mailto:a.verhagen@erasmusmc.nl)).

Paper submitted January 25, 2011; in revised form April 2, 2011; accepted April 3, 2011.

0161-4754/\$34.00

Copyright © 2011 by National University of Health Sciences.

doi:10.1016/j.jmpt.2011.04.007

pharmacological trials, while waiting list controls (WLCs) or pseudobehavioral interventions are often used in behavioral trials. The placebo and “no treatment” interventions intend to be less or ineffective because the specific effective element of the treatment has been removed. In most studies, the participants in both the active and “no treatment” or placebo groups tend to recover to some extent. This phenomenon can also be seen in patients with a chronic disease, like headache.<sup>7,8</sup> Research suggests that this effect is stronger for children than for adults.<sup>8</sup> These publications described the response in migraine trials; however, there is little evidence supporting such outcome in TTH patients.

The question remains whether the degree of recovery depends on the type of “no treatment” and/or placebo intervention in the control group. Although the intention of control interventions is to be relatively ineffective, the question rises as to what kinds of determinants might cause the improvement seen in these groups. The aim of this study was to describe and compare the observed effects, often called *placebo effects*, in the “no treatment” and placebo control groups in RCTs with TTH patients (adults and children) and children or adolescents with migraine.

## METHODS

### Design

This study was a secondary analysis of randomized clinical trials in an existing database of systematic reviews.

### Study Selection

A data set of 8 recent (2004-2010) systematic reviews on patients with TTH (adults and children) and migraine (only children and adolescents) was used, which included 197 original studies.<sup>9-16</sup> From this data set, RCTs with a “no treatment” or placebo control group were selected for review. Studies with missing data on the outcome measures were excluded.

The control groups included placebo medication, pseudobehavioral treatments, WLCs, and “no treatment” controls. Two authors (FG and AVB) screened the studies for inclusion. Disagreements on eligibility were solved by consensus or with a third author (AV).

### Risk of Bias

The original review authors assessed and scored the methodological quality of the RCTs according to the Delphi list.<sup>17</sup> The score from the original extraction forms is used; see the original reviews for the specific items with positive scores.<sup>9-16</sup>

### Data Extraction

Two review authors (FG and AVB) each performed data extraction for half of the RCTs and checked the data extraction for the other half. Consensus was reached in case of disagreement. The extracted information consisted of demographical data (age, sex), detailed description of the content of the control groups (number of participants and dropouts, intervention type, study design, duration of the intervention), results of the control groups on the relevant outcome measures, and the adverse events. The relevant outcome values were proportion of participants recovered, headache intensity, frequency and duration, pain free, headache index, rescue medication, and adverse events.

### Data Analysis

Based on the data presented in the original RCTs, the relative improvement (percentage) is calculated from baseline until posttreatment and from baseline until follow-up (if stated), only for the “no treatment” and placebo control groups. Furthermore, the proportion of recovered participants is calculated. Not every study reported all the outcome measures previously described. Therefore, our analysis is based on the data available in the included studies.

The control groups are split into 6 subgroups according to the intervention under study: Pharmacological trials were classified into (1) acute or (2) prophylactic placebo medication. Nonpharmacological trials were classified into (3) WLC groups; (4) pseudo-EMG biofeedback, pseudorelaxation, and pseudoacupuncture; (5) attention placebo control and discussion/information groups; and 6) “others.”

Furthermore, differences in recovery were analyzed between adults and children, parallel and crossover designs, and TTH and migraine. We assumed the outcome values to be normally distributed. Box plots were made to visualize the distribution of the different outcome values (weighted for sample size). Next, mean values and corresponding 95% confidence interval (CI) were calculated for different subgroups. To test for significant differences in responses between the 4 nonpharmacological subgroups, a 1-way analysis of variance with post hoc analysis was used. All the other comparisons were between 2 subgroups; so for these comparisons, an unpaired *t* test was used. A linear regression analysis was used to correct for confounders.

## RESULTS

### Data Set

Of the 197 RCTs from the original reviews, 131 had a “no treatment” or placebo control group (the list of studies is available upon request from the corresponding author). The remaining studies had control groups consisting of other medications or therapies (pragmatic trials). Eleven

publications had no sufficient data to calculate percentages for the “no treatment” or placebo control groups, and one other study had none of our selected relevant outcome measures. In total, 119 RCTs (85 on TTH and 34 on migraine) were included in our analysis (Fig 1), with a total of 7119 participants (5913 diagnosed with TTH and 1206 with migraine) in 131 “no treatment” or placebo control groups. The number of participants per group ranged from 4 to 447, with a mean of 54.3.

### Risk of Bias

The mean quality score of studies with a “no treatment” or placebo control group was 4.5 out of 10, compared with the mean quality score of 4.2 of the original data set. Overall, 42 studies (35.3%) were considered to be of high quality (or low risk of bias); 35 of these were pharmacological studies, and 7 were nonpharmacological studies.<sup>9-11,13-16</sup>

### Interventions

**Pharmacological Controls.** In pharmacological studies, 34 placebo control groups (n = 1017 participants) were found on prophylactic medication<sup>9,11,12,15</sup> and 44 placebo control groups (n = 5369) on acute medication.<sup>10,11,13</sup> In 57.7% of these 78 control groups, the placebo was described as “identical in shape or color” or “matching”; in 6.4%, the placebo was identical and had the same taste. In the remaining 35.9%, no specific description besides the word *placebo* was given.

**Nonpharmacological Controls.** In the nonpharmacological studies 53 “no treatment” control groups were found with a total of 733 participants. These were classified into 4 subgroups:

**Waiting List Controls.** In total, there were 20 control groups including a WLC (n = 279).<sup>11,12,14,16</sup> Participants in these studies were placed on a waiting list. In most of the cases, they were told that the treatment groups were temporarily filled and the treatment would start within 2 to 12 weeks. During this time, they had to fill in the headache diaries similar to the participants in the intervention group.

**Pseudo-EMG Feedback, pseudoacupuncture, or pseudo-relaxation.** In total, there were 13 control groups (n = 133) that received a treatment designed to be consistent with the therapy in the active treatment groups, but without the specific active elements of the treatment.<sup>9,11,12,14,16</sup> This enabled the researchers to control also for attention, expectations of improvement, information, contact with the investigator, and medical equipment. There were many forms of pseudo-EMG biofeedback. For instance, in some cases, the tone heard by the participants was not consistent with their tension level because it was previously recorded. They received no specific instructions, but had to reduce the level of

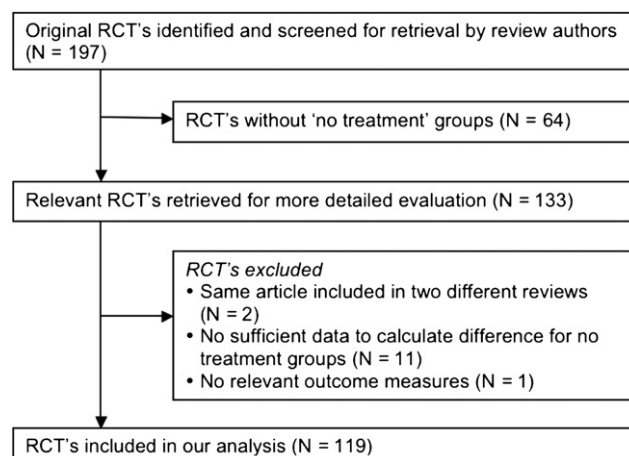


Fig 1. Flowchart.

tension by themselves, or were told that the tone would help them to relax by keeping out intruding thoughts.<sup>9,11</sup> In other cases, EMG was measured; but no feedback tone was given. Participants received instructions to relax or discuss their headache.<sup>11,12</sup> In one other study, participants received pseudoacupuncture during which the needles were inserted in the stratum corneum instead of the dermis.<sup>14</sup>

**Attention Placebo or Discussion Groups.** In total, 11 control groups (n = 194) were designed as attention placebo or discussion groups.<sup>11,12,14</sup> They mainly controlled for attention and time to be comparable with the intervention. In most studies, they received information on causes of headache and common triggers. They discussed psychological conflicts and stressful situations. In some cases, they received general or somewhat specific advice for coping skills.<sup>12,14</sup> In all the other cases, they received no advice.<sup>11,12,14</sup>

**“Others.”** In total, 10 control groups (n = 127) were classified as “others.”<sup>11,12,14,16</sup> In most of these studies, no treatment was given, nor were they placed on a waiting list. They had to self monitor through a headache diary.<sup>12,14</sup> In 3 studies, participants had to lie still for a certain amount of time. One study could not be placed in one of the former groups. In this study, participants were placed on a waiting list and received a pseudo-EMG measurement without feedback.<sup>11</sup>

### Outcome Measures

There was some variation between the different definitions of recovery. Most often, it was defined by the original study authors as 50% or more improvement of the complaints posttreatment or 50% or more improvement on the headache index. The definition of recovery as it was presented in the studies itself was used. Headache intensity

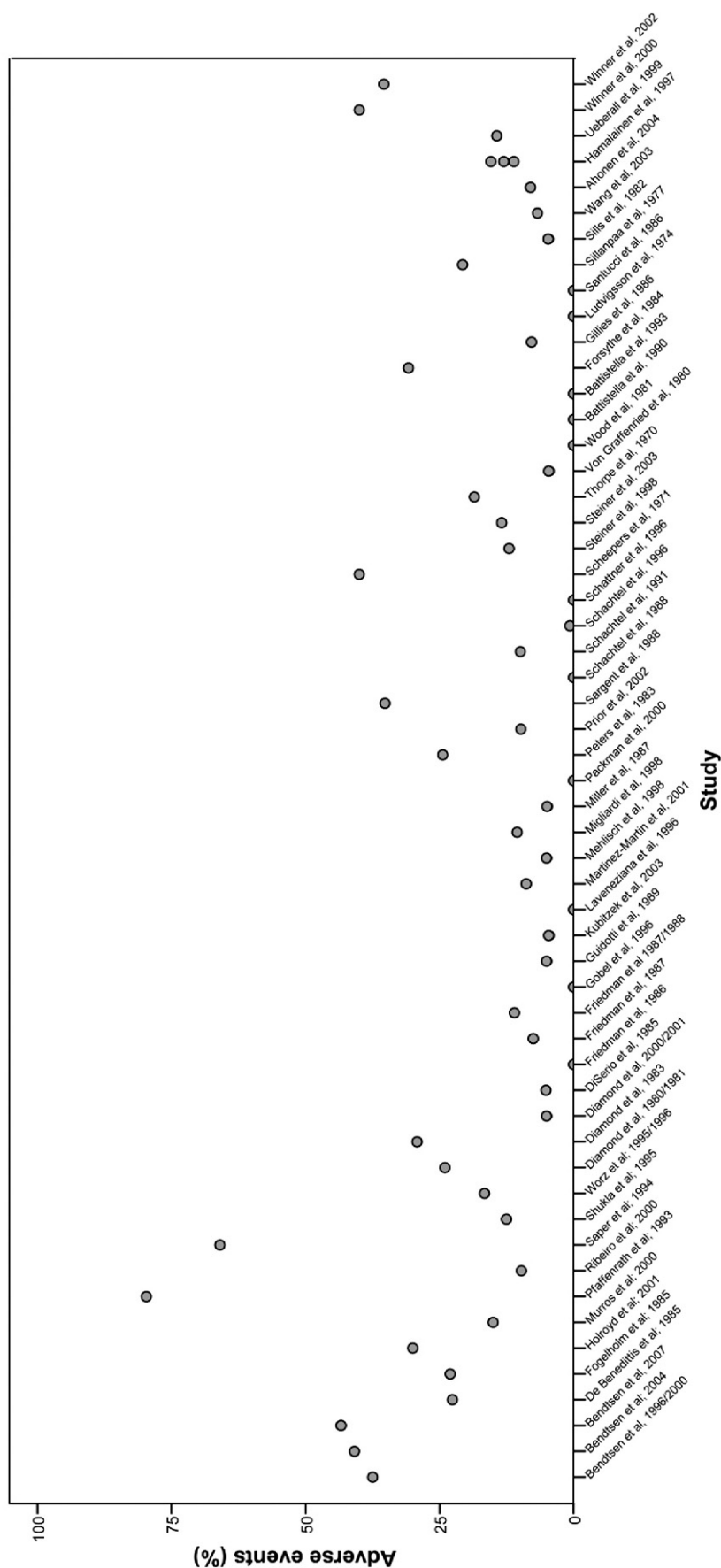


Fig 2. Proportion of participants with adverse events in pharmacological studies.



was rated on different scales, which varied between 3- and 11-point scales or visual analogue scales. Headache frequency and duration were also scored on different time units or point scales. A headache index was most often calculated as a product or sum of the headache frequency, duration, and intensity; but there were some variations. Some studies registered if participants rated themselves as being pain free. Frequently, this was measured as the proportion of participants that were pain free 2 hours after administration of the study medication. Rescue medication was measured as the proportion of participants that used analgesics if the study medication did not work, mostly within 2 hours after administration of the study drug. Adverse events were frequently measured. Sometimes, studies reported the number of participants with an adverse event; and in other cases, they reported the number of adverse events (which could be more than 1 per patient). We only used the number of participants as result.

### Recovery in the Control Groups

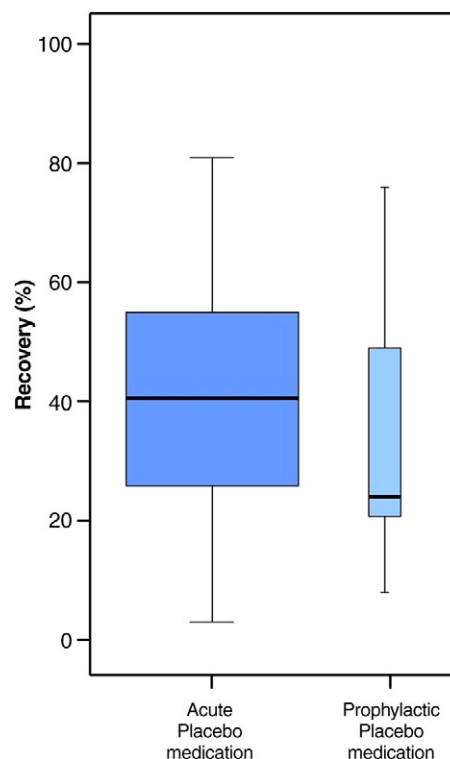
Overall, the mean recovery rate in the control groups was 35.7% (95% CI, 35.0-36.4).

**Pharmacological Studies.** In pharmacological studies, an average of 38.5% (95% CI, 37.8-39.3) of the participants in the control groups recovered and 21.8% (95% CI, 21.3-22.4) of the participants were pain free 2 hours after administration of the placebo medication. The mean use of rescue medication was 33.2% (95% CI, 32.4-33.9), and 12.7% (95% CI, 12.4-13) of the participants experienced adverse events (Fig 2). Most adverse events were minor complaints like tiredness, dry mouth, dizziness, or gastrointestinal complaints.

When the acute and prophylactic studies were separated, recovery was significantly higher in participants who used acute placebo medication (39.6%; 95% CI, 38.8-40.4) vs participants using prophylactic placebo medication (32.8%; 95% CI, 30.9-34.6) (Fig 3). The reduction in headache intensity was also significantly higher in the acute placebo group. Participants in the prophylactic control groups experienced significantly more adverse events than participants in the acute placebo group: 22.6% (95% CI, 20.8-24.3) vs 11.4% (95% CI, 11.1-11.6), respectively.

**Nonpharmacological Studies.** On average, 15.0% (95% CI, 13.5-16.6) of the participants recovered in the control groups of nonpharmacological studies. An improvement was found for headache intensity, frequency, and duration of 10.3% (95% CI, -12.3 to -8.3), 14.0% (95% CI, -15.9 to -12.0), and 9.7% (95% CI, -11.8 to -7.7), respectively.

Evaluating the difference in recovery between the 4 different types of control groups, a mean recovery rate was found in the WLC group of 17.9% (95% CI, 15.3-20.6); 8.4% (95% CI, 6.3-10.5) for the pseudobehavioral interventions; 18.3% (95% CI, 15.7-20.9) for the attention placebo groups; and 6.4% (95% CI, 3.8-9.0) for the “others” (Fig 4). Recovery rates were significantly higher in the



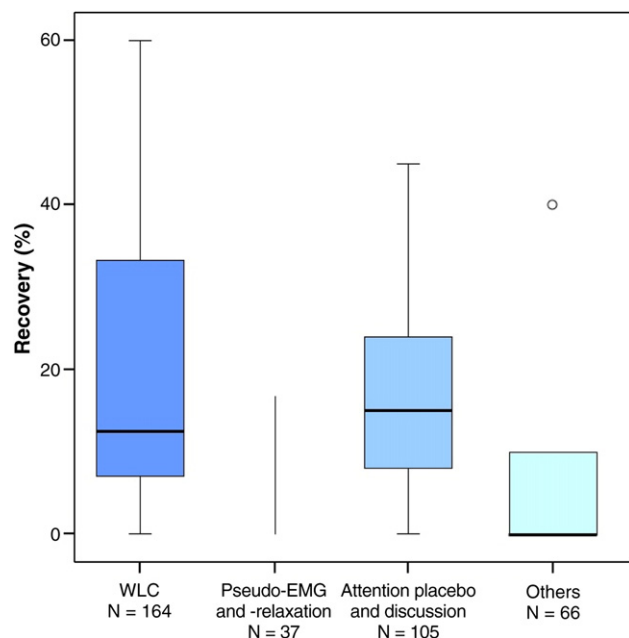
**Fig 3.** Box plot showing the difference in recovered participants between acute and prophylactic placebo, weighted by sample size. (Color version of figure is available online.)

WLC and attention placebo groups vs the “others” and the pseudobehavioral treatments.

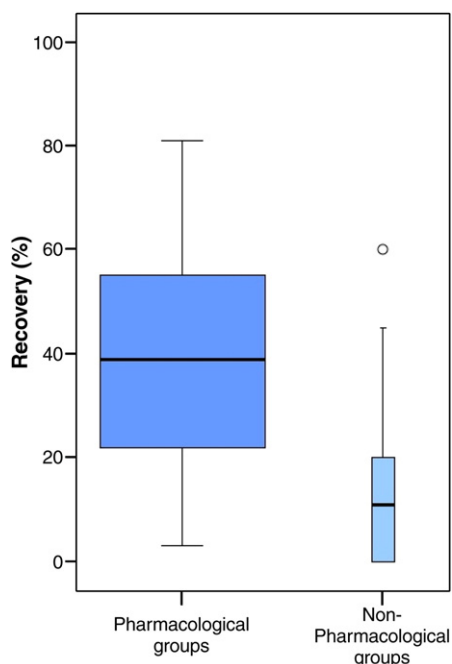
**Pharmacological vs Nonpharmacological Interventions.** The difference between the proportions of recovered participants in the control groups of pharmacological control groups (38.5%; 95% CI, 37.8-39.3) compared with the nonpharmacological control groups (15.0%; 95% CI, 13.5-16.6) is significant in favor of the pharmacological studies (Fig 5). This is also the case for the improvement in headache intensity, frequency, duration, and headache index, respectively. When the recovery rates were corrected for the quality scores of the studies, the difference between these groups became smaller, but was still significant.

**Adults vs Children.** No significant difference in recovery rates was found between adults and children in the total study population; but after correction for quality score, the difference in recovery rates became significant, although still small (35.4% in adults vs 37.7% in children).

When the control groups were split into pharmacological and nonpharmacological groups, adults were slightly more likely to recover in nonpharmacological studies: 17.7% (95% CI, 14.6-20.8) vs 14.1% (95% CI, 12.3-15.9) in children. In pharmacological studies, significantly more children recovered (also after correction for the quality score): 45.1% (95% CI, 44.0-46.2) of the children vs 36.5% (95% CI, 35.7-37.4) of the adults (Fig 6). After

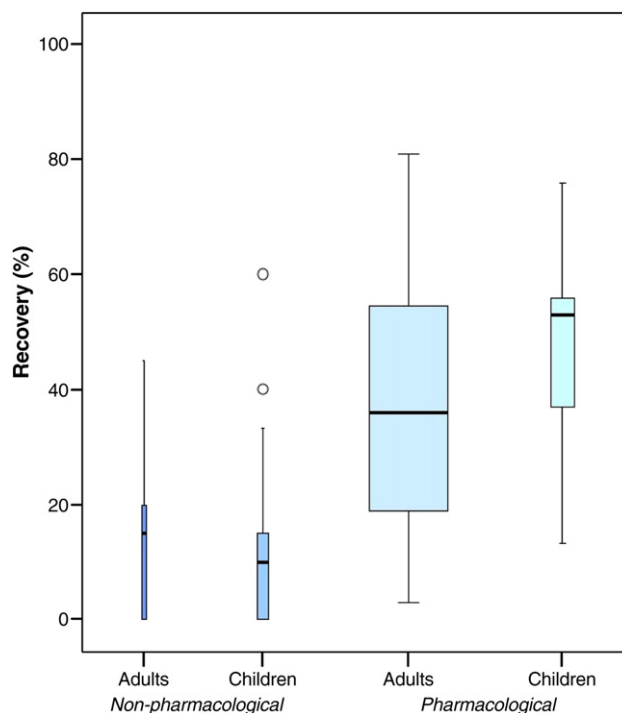


**Fig 4.** Box plot showing the difference in recovered participants between the 4 subgroups in the nonpharmacological studies; number of cases are given. (Color version of figure is available online.)



**Fig 5.** Box plot showing the difference in recovered participants in pharmacological and nonpharmacological control groups, weighted by sample size. (Color version of figure is available online.)

correction for quality score and type of intervention, there was a 6.9% (significant) difference in favor of children. This means that, overall, children have higher recovery rates compared with adults. Children also experienced significantly more adverse events than adults: 18.9% (95% CI,



**Fig 6.** Box plot showing the difference in recovered adults and children, classified into nonpharmacological and pharmacological control groups, weighted by sample size. (Color version of figure is available online.)

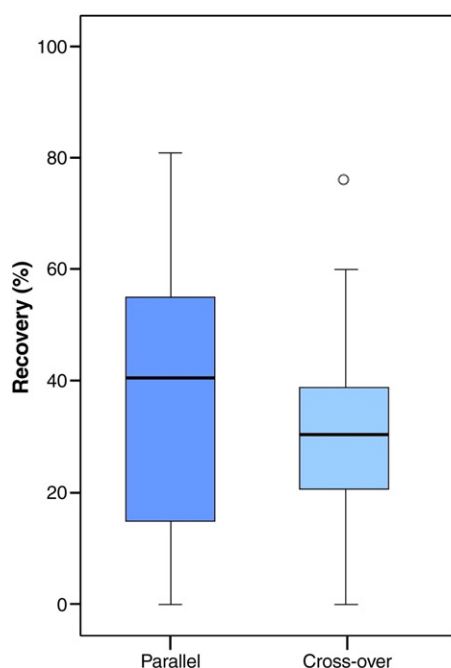
17.8-20.0) of the children vs 11.7% (95% CI, 11.4-12.0) of the adults.

**Study Design.** When the recovery rates in crossover design studies were compared with parallel group studies, a small but significant difference was found in recovery between parallel and crossover studies: 36.9% (95% CI, 36.0-37.7) vs 31.4% (95% CI, 30.2-32.6), respectively (Fig 7). From the parallel control groups, 22.4% (95% CI, 21.8-23.0) of the participants was pain free 2 hours after administration vs 19.7% (95% CI, 18.8-20.7) of the participants in crossover design studies.

**TTH vs Migraine.** The difference in recovery rates in the control groups was compared between TTH and migraine patients. The TTH patients had a mean recovery rate of 34.1% (95% CI, 33.2-34.9) vs 40.7% (95% CI, 39.5-42.0) of patients diagnosed with migraine, which is a significant difference. This was still the case when we corrected for the quality scores and the age of the participants.

## DISCUSSION

In our review, we found a mean recovery rate of 35.7% in the control groups; 34.1% of TTH patients improved vs 40.7% of the children and adolescents in migraine studies. Because there were no adults in the migraine studies, we corrected for age and found that the difference between TTH and migraine recovery increased and was still significant. A



**Fig 7.** Box plot showing the difference in recovered participants, classified into parallel group studies and crossover design studies, weighted by sample size. (Color version of figure is available online.)

possible explanation for this difference in recovery is the fact that migraine attacks have a shorter duration than TTH attacks. Therefore, the proportion of recovered participants due to natural course may be higher in migraine trials.

Overall, 21.8% of the patients were pain free 2 hours after medication administration. When we compared our results with other reviews, we found comparable effects: Bendtsen et al<sup>18</sup> found an average placebo response rate of 30% and a pain-free rate of 9%; Fernandes et al<sup>7</sup> found a 46% response rate in the control groups, whereas 21% was pain free; and Diener et al<sup>8</sup> also described similar outcomes from different studies. All of these studies described results gathered in migraine trials. We were unable to compare our results with trials that described the response for “no treatment” or placebo control groups in TTH patients.

There was a significantly higher recovery rate in the control groups in pharmacological trials compared with nonpharmacological trials (38.5% vs 15.0%). Reviews have shown that active pharmacological treatment is effective,<sup>10,13</sup> whereas the literature on the effectiveness of active prophylaxis and behavioral treatments is inconsistent or lacking.<sup>9,11,12,14,15</sup> Participants who received acute placebo medication recovered significantly more than participants who received prophylactic placebo medication, but the difference was small (7%). Diener et al<sup>8</sup> also found that the placebo response in acute migraine medication was higher than the response in prophylactic trials. A possible explanation for the difference in placebo response is the fact

that, in acute trials, participants have to take the study medication when they experience complaints, whereas, in prophylactic trials, they have to take the study medication on a continuous basis, even if they are symptom free.

In pharmacological trials, where a placebo is often used as a control, double blinding is possible. In these studies, patients having the expectation of receiving a real treatment might explain the higher recovery rates compared with the nonpharmacological trials. In nonpharmacological trials, blinding is often not possible.<sup>19</sup> In the WLC and attention placebo groups, significantly more participants recovered (17.9% and 18.3%) than in the pseudobehavioral groups or “others” (8.4% and 6.4%). In the group “others,” most participants received no treatment, nor were they placed on a waiting list; so they had no perspective of a future treatment. This and the natural fluctuation of headache probably might explain the difference in recovery between this group and the WLC.

We found a small but significant difference in recovery rates between adults and children in the total study population after correction for quality score (35.4% vs 37.7%). Children responded better in the pharmacological trials. This observation is in accordance with other studies.<sup>7,8,20</sup> Based on these studies, we also expected children to recover more in nonpharmacological trials; but we were unable to find support for these findings in our data. After correction, there was no longer a significant difference between adults and children in the nonpharmacological trials. The higher recovery rate in children could possibly be explained by their higher expectations.<sup>8</sup> Also, in migraine, attacks are known to be shorter in childhood. Therefore, when children in the “no treatment” or placebo control groups improve, their improvement is more likely a result of natural course than an effect of the study medication.<sup>7,20</sup>

The degree of recovery seemed to correspond with the study design: the recovery rate was significantly lower in crossover trials than in parallel group trials. This is probably related to the fact that participants in cross-over trials know that they are going to receive placebo at a certain time. This effect has also been described in prior studies.<sup>18,21,22</sup>

## Recommendations

In general practice (or family practice) as well as other health care professions, headache is a common complaint.<sup>1,23,24</sup> In the Netherlands, the standard pharmacological treatment according to the general practice guideline is to start with analgesics like acetaminophen or nonsteroidal anti-inflammatory drugs in the case of TTH.<sup>25</sup> In the case of children with migraine, the first step is a combination of an analgesic with an antiemetic.<sup>1,26</sup> Pharmacological treatment starts when nonpharmacological treatments like lifestyle changes, relaxation therapy, cognitive therapy, and reassurance did not work.<sup>25</sup> Many of these prescribed (or over-the-counter) medications,



mainly nonsteroidal anti-inflammatory drug, may lead to adverse events and can cause medication overuse headache. Considering these risks, we recommend that the prescription of medication needs to be carefully considered and evaluated with each individual patient. Because of our recovery results in “no treatment” control groups in pharmacological trials, the question rises whether or not this way of prescription is always preferable over no treatment (wait and see) especially in the TTH population. Our results of the placebo response are not comparable to “wait and see” in general practice because a part of this placebo response could be attributed to the expectations of the participants, who believed that they received an active treatment. On the other hand, a placebo cannot easily be prescribed in daily clinical practice.

During our research, we also found studies that compared behavioral treatment with a pseudobehavioral treatment. As described before, there was a wide variety of these control groups. This raises the question whether or not some of them are plausible for patients, for example, in the case of studies where patients only had to lie still on a bed for 10 minutes.<sup>16</sup> On the other hand, most “no treatment” control groups in nonpharmacological studies had elements of real treatment like attention, information, and hope for recovery. In the case of pseudobehavioral treatments, the participants believed they received an active treatment. Therefore, none of these “no treatment” control groups were absolute no treatment and were not completely generalizable to daily practice. The “no treatment” control groups in future studies should be carefully and precisely defined because our study shows that “no treatment” is open to many interpretations.

## Limitations

Our results may have been influenced by several shortcomings. First, the different studies used a wide variety of outcome measures, scales, time intervals, and chosen end point measures. We tried to group and to compare the variables as best as possible and preferably used the ones that were used most frequently. A robust outcome variable as “pain free” would have been a desirable outcome measure because of the clear definition. However, not many studies used pain-free status as outcome variable. Therefore, mostly “recovery” was chosen as outcome, based on different rating scales.

Second, all included studies were published before 2005. When information was missing or when studies showed inconsistent results, we did not contact the authors for additional information. This might have led to bias. However, most trials were published between 1980 and 2000. Therefore, it would be impossible to contact all of them; and the question remains if this retrieved information would have led to less bias.

Third, the overall study quality was low; only 35.3% of all the trials had low risk of bias. In general, pharmacological trials have shown a higher quality score and also a higher recovery rate in the “no treatment” or placebo control groups.

Fourth, comparing different control groups, the number of cases of the outcome variable at interest varied widely. For instance, when we compared the 4 different subgroups in the nonpharmacological studies, we found data on recovery for only 37 participants of the original 133 in the pseudobehavioral group compared with data of 164 participants of the original 279 in the WLC group. The number of missing cases varied widely for the different comparisons. Because of this fact, looking at the box plots symmetry, one can see that some of them are well shaped, whereas others are not symmetrical, although we assumed that they were all normally distributed. Our results may therefore be biased as a consequence of the low number of cases in some of the calculations. Also, because of the nonnormality of the distributions of the results in some of the subgroups, our results may not be generalizable to the general population or the population of adults with migraine. However, our results considering the pharmacological studies are comparable to the current literature on migraine. We were unable to compare our results with literature concerning placebo response in TTH patients, so further investigation should be aimed at this particular subgroup. Fifth, when necessary, we corrected for the confounders age and quality score because they varied widely throughout the included trials and might have affected the outcome. Finally, treatment effects of headache are complex; thus in future investigations, new models should be considered.<sup>27</sup>

## CONCLUSION

This study showed a relatively high overall recovery rate in the “no treatment” or placebo control groups (35.7%). Control groups in pharmacological trials showed a higher response rate than nonpharmacological trials (38.5% vs 15.0%), and children had a higher recovery rate than adults in pharmacological trials (45.1% vs 36.5%). Recovery rates in control groups in acute medication trials seemed to be higher compared with prophylactic trials (39.6 vs 32.8). Participants in waiting list and attention placebo control groups recovered more than those in the other nonpharmacological control groups (17.9% and 18.3% vs 8.4% and 6.4%). With all studies combined, participants in control groups of parallel trials showed a higher recovery rate than the participants in crossover trials (36.9% vs 30.4%); and migraine patients recovered more than TTH patients (40.7% vs 34.1%).

Notably, the diversity of the design of “no treatment” control groups was large; therefore, the label of “no treatment” is open to many interpretations.

### Practical Applications

- The mean recovery rate in the control groups was 35.7%.
- The recovery rate in the control groups varied substantially between type of intervention evaluated.
- The recovery rate in pharmacological control groups is significantly higher compared to the recovery rate in non-pharmacological control groups.

### ACKNOWLEDGMENT

The authors thank Ben Bode, Hester van Eeren, and Rick de Vos for their input on this manuscript.

### FUNDING SOURCES AND POTENTIAL CONFLICTS OF INTEREST

No funding sources or conflicts of interest were reported for this study.

### REFERENCES

1. Mannix LK. Epidemiology and impact of primary headache disorders. *Med Clin North Am* 2001;85:887-95.
2. Pinto A, Arava-Parastatidis M, Balasubramaniam R. Headache in children and adolescents. *J Can Dent Assoc* 2009;75:125-31.
3. Silberstein SD, Lipton RB. Headache epidemiology. Emphasis on migraine. *Neurol Clin* 1996;14:421-34.
4. Bille B. A 40-year follow-up of school children with migraine. *Cephalalgia* 1997;17:488-91.
5. Speciali JG, Eckeli AL, Dach F. Tension-type headache. *Expert Rev Neurother* 2008;8:839-53.
6. Headache Classification Committee of the International Headache Society. The international classification of headache disorders. *Cephalalgia* 2004;24:1-152.
7. Fernandes R, Ferreira JJ, Sampaio C. The placebo response in studies of acute migraine. *J Pediatr* 2008;152:527-33, 33e1.
8. Diener HC, Schorn CF, Bingel U, Dodick DW. The importance of placebo in headache research. *Cephalalgia* 2008;28:1003-11.
9. Verhagen A, Damen L, Berger M, Passchier J, Koes B. Lack of benefit for prophylactic drugs of tension-type headache in adults: a systematic review. *Fam Pract* 2010;27:151-65.
10. Verhagen AP, Damen L, Berger MY, Passchier J, Merlijn V, Koes BW. Is any one analgesic superior for episodic tension-type headache? *J Fam Pract* 2006;55:1064-72.
11. Verhagen A, Damen L, Berger M, Passchier J, Koes B. Behavioral treatments of chronic tension-type headache in adults: are they beneficial? *CNS Neurosci Ther* 2009;15:183-205.
12. Verhagen A, Damen L, Berger M, Passchier J, Merlijn V, Koes B. Conservative treatments of children with episodic tension-type headache. A systematic review. *J Neurol* 2005;252:1147-54.
13. Damen L, Bruijn J, Verhagen AP, Berger M, Passchier J, Koes BW. Symptomatic treatment of migraine in children: a systematic review of medication trials. *Paediatrics* 2005;116:295-302.
14. Damen L, Bruijn J, Koes B, Berger M, Passchier J, Verhagen A. Prophylactic treatment of migraine in children. Part 1. A systematic review of non-pharmacological trials. *Cephalalgia* 2005;26:373-83.
15. Damen L, Bruijn J, Verhagen A, Berger M, Passchier J, Koes B. Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials. *Cephalalgia* 2005;26:497-505.
16. Lenssinck ML, Damen L, Verhagen AP, Berger MY, Passchier J, Koes BW. The effectiveness of physiotherapy and manipulation in patients with tension-type headache: a systematic review. *Pain* 2004;112:381-8.
17. Verhagen A, de Vet H, de Bie R, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;51:1235-41.
18. Bendtsen L, Mattsson P, Zwart JA, Lipton RB. Placebo response in clinical randomized trials of analgesics in migraine. *Cephalalgia* 2003;23:487-90.
19. Rains JC, Penzien DB. Behavioral research and the double-blind placebo-controlled methodology: challenges in applying the biomedical standard to behavioral headache research. *Headache* 2005;45:479-86.
20. Lewis DW, Winner P, Wasiewski W. The placebo responder rate in children and adolescents. *Headache* 2005;45:232-9.
21. Hanten WP, Olson SL. The effectiveness of CV-4 and resting position techniques on subjects with tension-type headaches. *J Man Manip Ther* 1999;7:64-70.
22. Hoyt WH, Shaffer F. Osteopathic manipulation in the treatment of muscle-contraction headache. *J Am Med Assoc* 1979;78:322-5.
23. Vavrek D, Haas M, Peterson D. Physical examination and self-reported pain outcomes from a randomized trial on chronic cervicogenic headache. *J Manipulative Physiol Ther* 2010;33:338-48.
24. Vernon H, Jansz G, Goldsmith CH, McDermaid C. A randomized, placebo-controlled clinical trial of chiropractic and medical prophylactic treatment of adults with tension-type headache: results from a stopped trial. *J Manipulative Physiol Ther* 2009;32:344-51.
25. Knuistingh Neven A, Bartelink MEL, De Jongh TOH, Ongerling JEP, Oosterhuis WW, et al. Huisarts Wet 2004; 46:411-22.
26. Hershey AD. Current approaches to the diagnosis and management of paediatric migraine. *Lancet Neurol* 2010;9:190-204.
27. Haas M, Aickin M, Vavrek D. A preliminary path analysis of expectancy and patient-provider encounter in an open-label randomized controlled trial of spinal manipulation for cervicogenic headache. *J Manipulative Physiol Ther* 2010;33:5-13.